PATENT COOPERATION TREATY
EUROPEAN PATENT OFFICE

In re PCT APPLICATION of	
GILEAD SCIENCES, INC. et al.	Agent's File Ref. 588.F
International Application No. : PCT/US2004/043969	
International Filing Date: 29 December 2004	
For: PHOSPHONATES, MONOPHOSPHONAMIDATES, BISPHOSPHONAMIDATES FOR THE TREATMENT OF VIRAL DISEASES	

International Preliminary Examining Authority
European Patent Office
Erhardtstrasse 27
D-80298 Munich
Germany

SUPPLEMENTAL RESPONSE TO THE WRITTEN OPINION OF THE ISA

Dear Sir:

This is further to the International Search Report and Written Opinion of the ISA, mailed May 19, 2005, and applicants' response thereto which was submitted with the Demand on October 27, 2005.

Applicants have noted that the certain of the compound claims in the replacement claim set submitted with the response of October 27 failed to distinguish the Keith et al. paper D2, which discloses (isopropyl L-alaninyl)phenyl PME-N6-(cyclopropyl) DAP and bis(butyl L-alaninyl) PME-N6-(cyclopropyl)DAP. D2 teaches the use of these two compounds in the treatment of orthopoxvirus infection. Keith et al. do not teach or suggest the use of these two compounds for the treatment of tumors or HPV infection.

Accordingly, applicants have further revised the claims. The compound claims are now claims 57-61, with the remainder being directed to the novel uses of compounds as set forth in claims 1-56.

The basis for the uses recited in claim 1 includes specification page 30, line 17, Table 79-4 page 120 and the original claims. Claim 35 has been amended to recite that the treatment is of an HPV positive carcinoma cell (basis includes Table 80-4). Claim 36 now recites treatment of an HPV negative carcinoma cell (basis includes Table 79-4). New claims 60-62 are directed to an additional compound found on page 49 (compound 10).

In summary, original claims 1-130 have been replaced in their entirety by new claims 1-62.

Applicants wish to bring to the examiner's attention several additional citations. These are Becker et al., US 2003/0219727; Hatse et al. *Biochem. Pharm.* 58:311-323 (1999); Rose et al. *J. Nat. Cancer Inst.* 82(6):510-512 (1990); and Compton et al. *Biochem. Pharm.* 58:709-714 (1999).

The amended claims are now believed to be novel and possess inventive step over the references of record.

Respectfully submitted,

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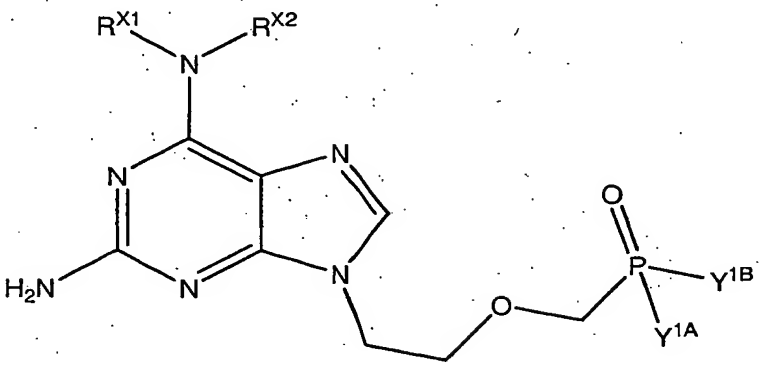
Date: December 9, 2005

Attached: Amendments to the claims; 4 citations

What Is Claimed:

1. The use of a compound Formula I, in the preparation of a medicament for the treatment of HPV or tumor cells



I

wherein:

Y^{1A} and Y^{1B} are independently Y^1;

R^{X1} is H and R^{X2} is W^5;

Y^1 is =O, -O(R^X), =S, -N(R^X), -N(O)(R^X), -N(OR^X), -N(O)(OR^X), or -N(N(R^X)(R^X)) provided that at least one Y^1 is –N(R^X);

R^X is independently R^1, R^2, R^4, W^3, or a protecting group;

R^1 is independently -H or alkyl of 1 to 18 carbon atoms;

R^2 is independently R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is -H, -F, -Cl, -Br, -I, $-CF_3$, -CN, N_3, $-NO_2$, or $–OR^4$;

R^{3b} is =O, -O(R^4), =S, -N(R^4), -N(O)(R^4), -N(OR^4), -N(O)(OR^4), or -N(N(R^4)(R^4));

R^{3c} is $-R^4$, $-N(R^4)(R^4)$, $-SR^4$, $-S(O)R^4$, $-S(O)_2R^4$, $-S(O)(OR^4)$, $-S(O)_2(OR^4)$, $-OC(R^{3b})R^4$, $-OC(R^{3b})OR^4$, $-OC(R^{3b})(N(R^4)(R^4))$, $-SC(R^{3b})R^4$, $-SC(R^{3b})OR^4$, $-SC(R^{3b})(N(R^4)(R^4))$, $-N(R^4)C(R^{3b})R^4$, $-N(R^4)C(R^{3b})OR^4$, $-N(R^4)C(R^{3b})(N(R^4)(R^4))$, W^3 or $-R^5W^3$;

R^{3d} is $-C(R^{3b})R^4$, $-C(R^{3b})OR^4$, $-C(R^{3b})W^3$, $-C(R^{3b})OW^3$ or $-C(R^{3b})(N(R^4)(R^4))$;

R^4 is -H, or an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2 to 18 carbon atoms;

W^3 is W^4 or W^5;

W^4 is R^6, $-C(R^{3b})R^6$, $-C(R^{3b})W^5$, $-SO_{M2}R^6$, or $-SO_{M2}W^5$, wherein R^6 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups; and

M2 is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

2. The use of claim 1 wherein Y^{1A} and Y^{1B} are $-N(R^X)$.

3. The use of claim 2 wherein R^X is R^2.

4. The use of claim 3 wherein R^2 is R^4 substituted with R^{3d}.

5. The use of claim 4 wherein R^4 is ethyl substituted with R^{3d}.

6. The use of claim 5 wherein R^{3d} is $-C(R^{3b})OR^4$.

7. The use of claim 6 wherein R^{3b} is =O.

8. The use of claim 7 wherein R^4 is alkyl of 1 to 18 carbon atoms.

9. The use of claim 1 wherein R^{3d} is $-C(R^{3b})OW^3$.

10. The use of claim 1 wherein R^4 is propyl substituted with R^{3d}.

11. The use of claim 1 wherein R^{3d} is $-C(R^{3b})OR^4$.

12. The use of claim 3 wherein R^2 is R^4 independently substituted with two R^3 groups.

13. The use of claim 12 wherein R^4 is methyl substituted with two R^3 groups.

14. The use of claim 13 wherein one R^3 group is R^{3c}.

15. The use of claim 1 wherein R^5 is methylene.

16. The use of claim 1 wherein W^3 is W^5.

17. The use of claim 14 wherein one R^3 group is R^{3d}.

18. The use of claim 1 wherein R^{3c} is W^3.

19. The use of claim 1 wherein Y^{1A} is $-N(R^X)$ and W^5 is a carbocycle.

20. The use of claim 1 wherein Y^{1B} is $-N(R^X)$.

21. The use of claim 1 wherein R^{3c} is $-R^5W^3$.

22. The use of claim 16 wherein W^5 is a carbocycle.

23. The use of claim 1 wherein Y^{1B} is $-O(R^X)$.

24. The use of claim 23 wherein Y^{1B} is $-O(W^3)$.

25. The use of claim 22 wherein said carbocycle is phenyl.

26. The use of claim 1 wherein R^2 is R^4 substituted with R^{3c} and R^{3d}.

27. The use of claim 26 wherein R^4 is ethyl substituted with R^{3c} and R^{3d}.

28. The use of claim 1 wherein Y^{1A} and Y^{1B} are $-O(R^X)$.

29. The use of claim 1 wherein R^{X2} is R^4.

30. The use of claim 1 wherein R^2 is R^4 substituted with one R^3.

31. The use of claim 30 wherein R^4 is methyl substituted with one R^3.

32. The use of claim 31 wherein R^3 is R^{3a}.

33. The use of claim 32 wherein R^{3a} is $-CF_3$.

34. The use of claim 30 wherein R^4 is $-CH_2-CF_3$.

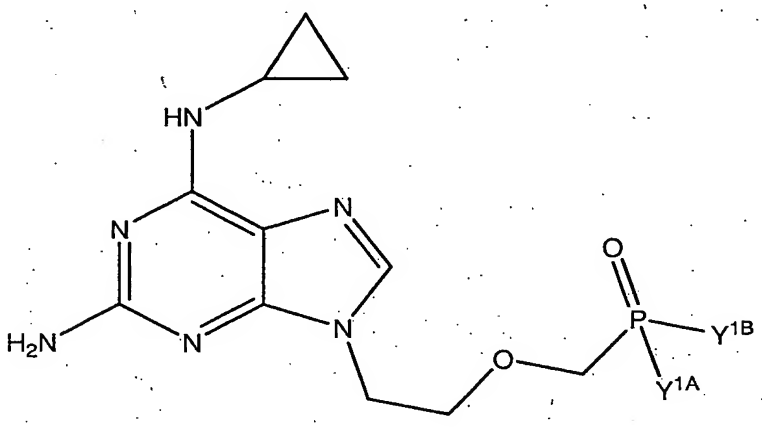
35. The use of claim 1 wherein the treatment is of an HPV positive carcinoma cell.

36. The use of claim 1 wherein the treatment is of an HPV negative carcinoma cell.

37. The use of claim 1 wherein the treatment is of a patient infected with HPV.

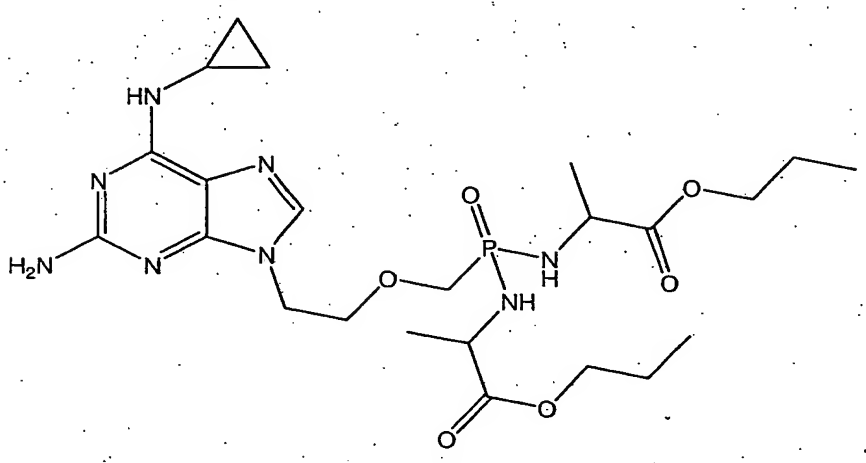
38. The use of claim 1 wherein the treatment is topical.

39. The use of claim 1 wherein the compound is of Formula IA,

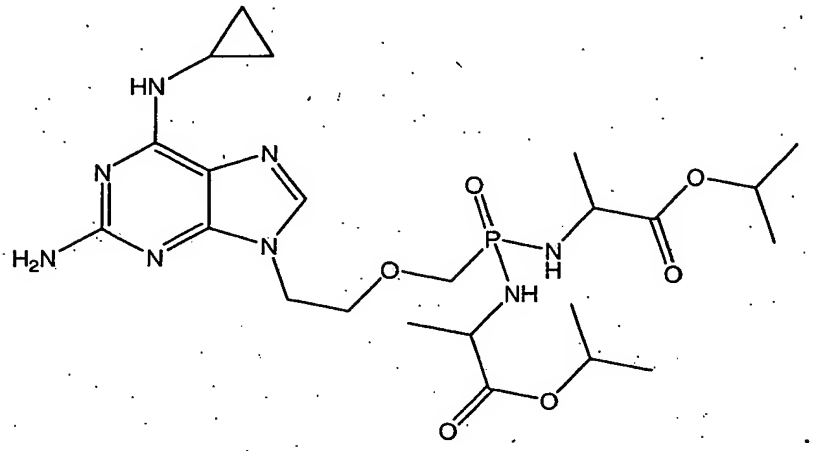


IA

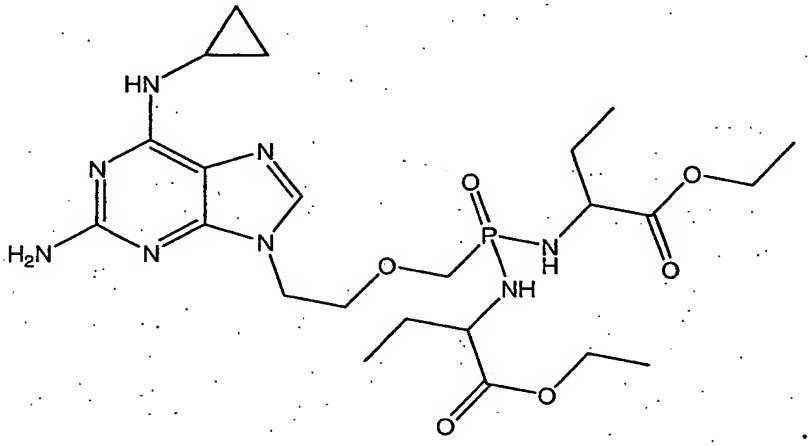
40. The use of claim 1 wherein the compound is of the formula,



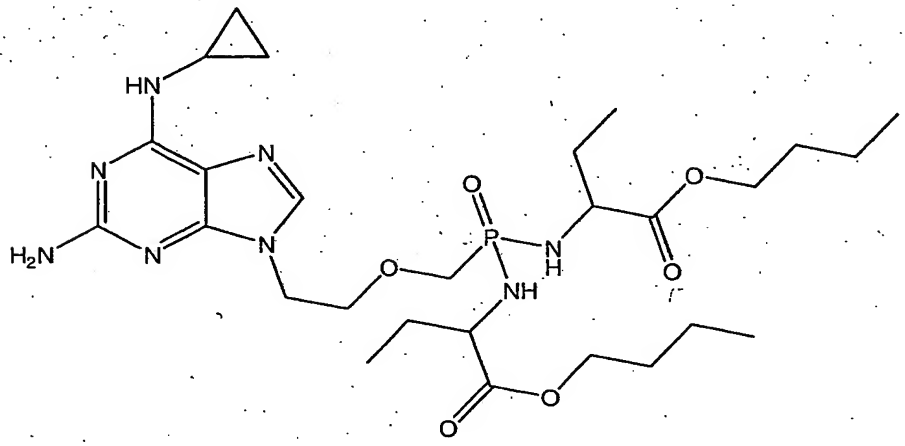
41. The use of claim 1 wherein the compound is of the formula,



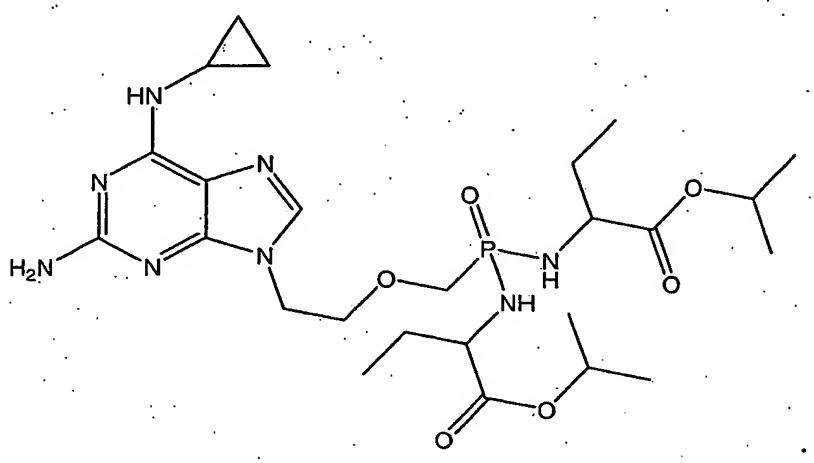
42. The use of claim 1 wherein the compound is of the formula,



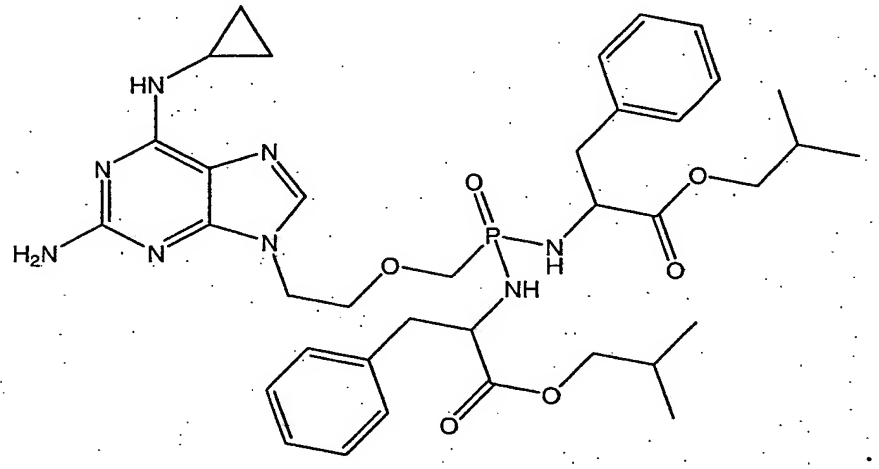
43. The use of claim 1 wherein the compound is of the formula,



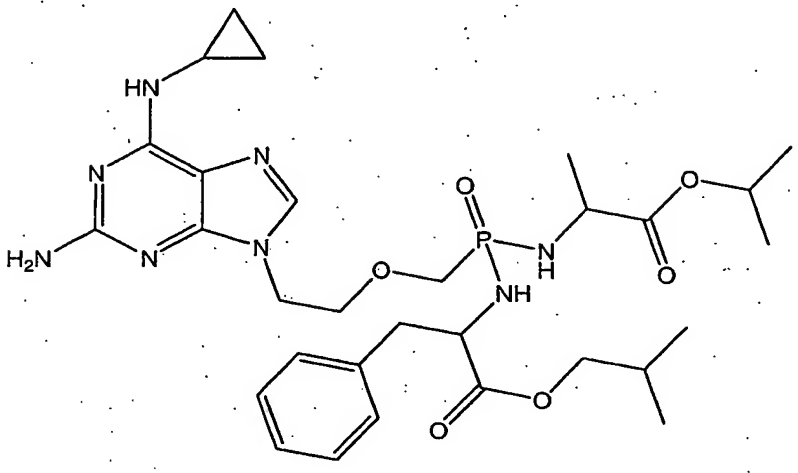
44. The use of claim 1 wherein the compound is of the formula,



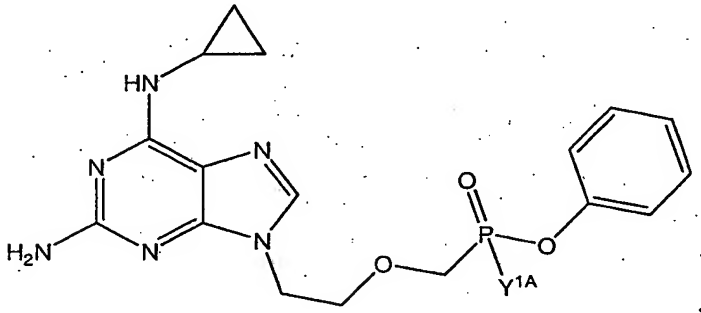
45. The use of claim 1 wherein the compound is of the formula,



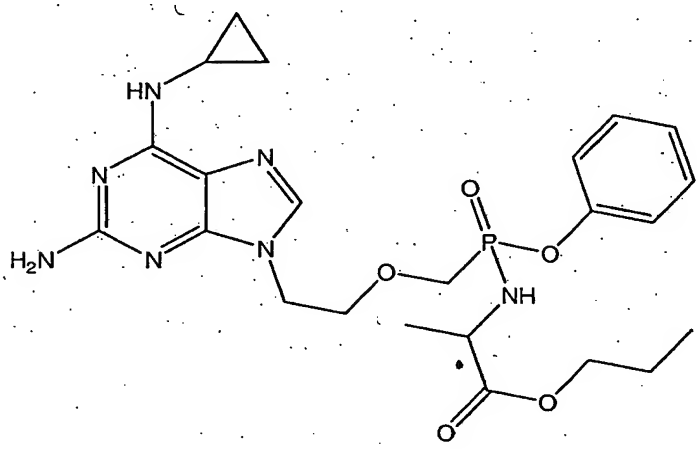
46. The use of claim 1 wherein the compound is of the formula,



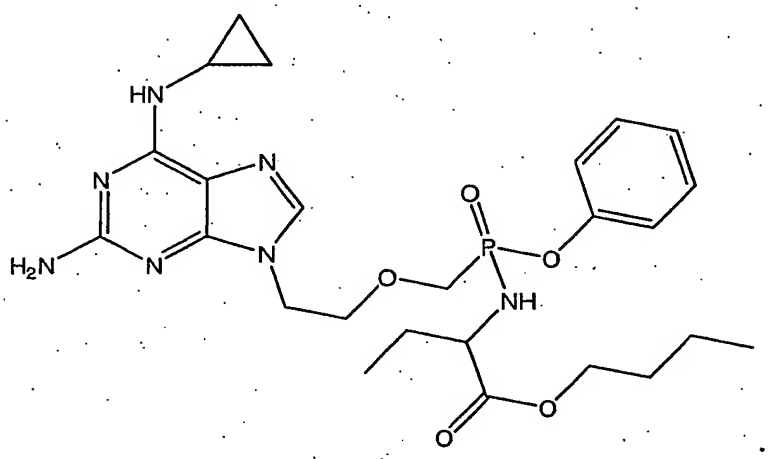
47. The use of claim 1 wherein the compound is of the formula,



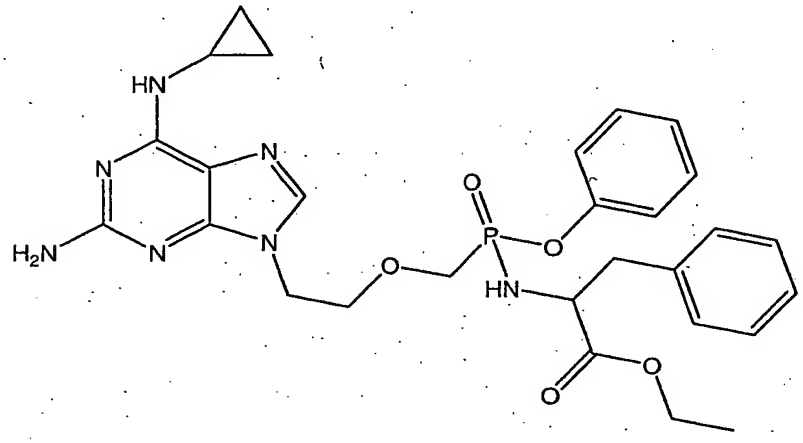
48. The use of claim 1 wherein the compound is of the formula,



49. The use of claim 1 wherein the compound is of the formula,



50. The use of claim 1 wherein the compound is of the formula,



51. The use of claim 1 wherein the medicament is a pharmaceutical composition comprising an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

52. The use of claim 51 wherein the medicament is a gel composition.

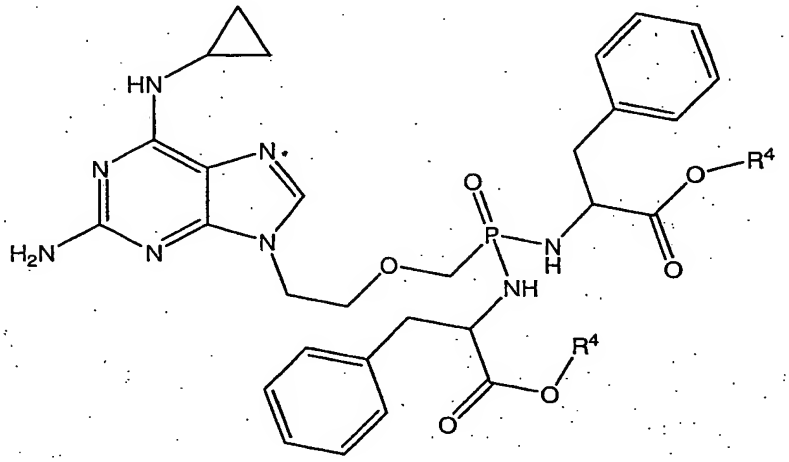
53. The use composition of claim 51, wherein said medicament is an ointment composition.

54. A use of claim 1 wherein the medicament comprises an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, an effective amount of at least one antiviral agent, and a pharmaceutically acceptable carrier.

55. The use of claim 54, where said medicament is a gel composition.

56. The use of claim 54, where said medicament is an ointment composition.

57. A compound of the formula,

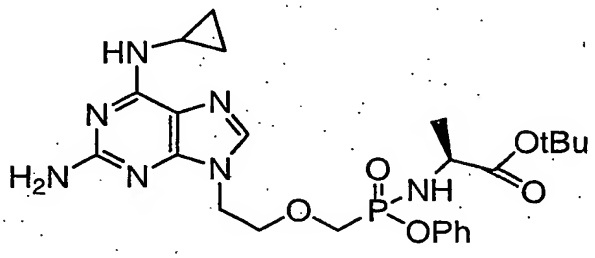


wherein R^4 is H, or an alkyl of 1 to 18 atoms, alkenyl of 2 to 18 carbon atoms or alkynyl of 2 to 18 carbon atoms and pharmaceutically acceptable salts thereof.

58. A gel or ointment comprising the compound of claim 57.

59. The use of the compound of claim 57 in the preparation of a medicament for use as an antiproliferative, apoptotic or anti-HPV agent.

60. A compound having the formula



61. The compound claim 60 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

62. The use of the compound of claim 60 in the preparation of a medicament for the treatment of a tumor.